REMARKS

Entry of the preceding amendments and consideration of the comments which follow are respectfully requested by Applicants.

Amendments to claims

Claims 1, 15, 19, and 22 have been amended. Claim 14 has been canceled. Support for the amendment to claim 1 is found in original claim 14. No new matter has been added.

Claims 4-11 and 23-26 are withdrawn. Claims 1-3, 12, 13, and 15-22 remain pending for examination.

Oath/Declaration

The Examiner notes that the oath or declaration filed on 7/21/04 is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration. Applicants are filing concurrently herewith a new declaration that avoids the error, and they respectfully request the Examiner's reconsideration.

Rejection under 35 USC §112, second paragraph

Claim 15 is rejected as being indefinite due to the recitation of "the building blocks" in line 1. Specifically, the Examiner asserts that there is insufficient antecedent basis for this limitation in the claim. The Examiner notes that claim 1 recites both monomeric and oligomeric building blocks, but that the general structural formula I or II of claim 15 refers only to monomeric building blocks so that it is unclear as to which "building blocks" are referred to by the term in claim 1.

Claim 15 is amended to specify that the nucleotide building blocks referred to therein are monomeric. Hence, claim 15 is a proper dependent claim to claim 1 as it narrows the scope accordingly. The rejection of claim 15 under §112 as being indefinite is therefore overcome, and reconsideration is respectfully requested.

Claim 19 is rejected as being indefinite for the recitation of "R3" in line 1. Specifically the Examiner asserts that there is no antecedent basis since claim 12, the base claim from which claim 19 depends, does not recite an "R3." Applicants appreciate the Examiner bringing this inadvertent typographical error to their attention. Claim 19 is meant to depend from claim 18, which clearly recites

the antecedent R3, and claim 19 has been amended accordingly. Reconsideration is therefore respectfully requested.

Claim 22 is rejected as being indefinite for the recitation "analogs thereof, and analogs containing additional amino groups," because, according to the Examiner, it is not clear to which entities the term "analogs" is referring. Claim 22 is amended to clarify that "aza analogs," "deaza analogs," and "analogs thereof containing additional amino groups" are groups of analogs of each of the three listed bases. Applicants submit that, as amended, the recitation of claim 22 is clear on this point, and reconsideration is therefore respectfully requested.

Rejection under 35 USC §102

Claims 1-3, 12, and 13 are rejected under 35 USC §102(b) as being anticipated by McGall et al., US 6,238,862 ("McGall"). Specifically, the Examiner asserts that McGall teaches methods for quality control in manufacturing nucleic acid probe arrays including synthesizing nucleic acids using protected monomers, de-protecting or removal of the protecting group, and determining the amount of unprotected active sites by detecting the amount of cleaved detectable label. The Examiner further asserts that McGall teaches that the protecting label may be a fluorescent label, and that the fluorescent label is linked to the nucleotide, and that McGall teaches linking the fluorescent label through the phosphate group in the sugar of the nucleotide. This rejection is traversed.

Instant independent claim 1 recites a quality control method for manufacturing a biopolymer array comprising (a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups, (b) cleaving off the detectable protecting groups, and (c) carrying out a determination of the detectable protecting groups on the array after cleavage in order to determine the efficacy of deprotection, wherein at least some of the detectable protecting groups couple to and protect amino groups of nucleobases.

McGall, while being directed to quality control methods for oligonucleotide arrays, limits the linking chemistry aspect of the disclosed methods to the activated hydroxyl groups (e.g. column 5, generally lines 14-20) of the oligonucleotides. McGall teaches detectable protecting groups specifically for protecting the 5'-hydroxyl group and uses this detectable protecting group for determining the synthesis efficiency of the DNA synthesis array and for determining the amount of unprotected active sites on the oligonucleotide array. However, this is solely with respect to the 5'-hydroxy functionality. McGall fails to teach or suggest detectable protecting groups for protecting other active sites on the

oligonucleotides such as the nucleobase amino groups as presently disclosed and recited. Complete deprotection of the nucleobase amino groups is essential, as presently taught, for optimal application of the chip (array), since, for example, formation of Watson-Crick or Hoogsteen base pairs may be inhibited in a subsequently desired hybridization (specification page 3, lines 3-6). McGall fails to teach or disclose quality control methods where the nucleobase amino active group is implicated. Hence, the present quality control methods are distinguished over McGall by the greater scope of the quality ascertained, rendering the tested arrays suitable for a wider variety of applications.

Anticipation under 35 USC §102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). McGall fails to teach quality control methods comprising, inter alia, monomeric or oligomeric building blocks comprising detectable protecting groups wherein at least some of the detectable protecting groups couple to and protect amino groups of nucleobases, as presently recited. McGall teaches methods which rely only on protection of the 5' hydroxy active site and therefore, quality of the array with respect to subsequent reactions which implicate the amino groups is not assessed. Hence, the present methods cannot be anticipated by McGall, and the rejection of claims 1-3, 12 and 13 under 35 USC §102 is overcome. Reconsideration is respectfully requested.

Claims 1-3 and 12-22 are rejected under 35 USC §102(b) as being anticipated by Wagner et al., Helv. Chim. Acta Vol. 80:200-212, 1997 ("Wagner"). Specifically, the Examiner asserts that Wagner discloses methods of nucleic acid synthesis using protected nucleotides and teaches synthesis of various oligonucleotides using protected nucleotides, deprotection of the nucleotides through removal of the protecting groups, and kinetic studies of the deprotection process. The Examiner further asserts that the reference teaches a fluorescent label as the detectable label that may be linked directly to the nucleobase through the amino group.

Instant claim 1 is set forth in detail, above.

Applicants acknowledge that Wagner discloses a nucleobase amino protecting group that may or may not exhibit detectable fluorescence. The protecting group of Wagner is a chlorinated dansyl, but Wagner neither teaches nor relies upon its potential fluorescent properties and does not indicate that the protecting group is detectable via any quantity of fluorescence that may be characteristic of this group. Applicants submit that the Examiner offers no support for the contention that dnseoc either fluoresces or fluoresces to any extent detectable for purposes of the present methods. On the contrary, the kinetic studies of Wagner, cited by the Examiner as equivalent to step (c) of instant claim 1, rely on typical

HPLC technology, which is not suitable for the on-chip or "on the array" analysis required by instant claim 1. Indeed, Applicants teach that advantages of the present invention over other disclosed technologies, including Wagner, comprise providing the capability of quality control with respect to completeness of deprotection of the biopolymer active sites on the chip without destruction of any biopolymer and without the need for further steps once the final deprotection or detection has been carried out (see, e.g., paragraphs [0005] and [0007]).

Wagner discloses nucleobase amino protection groups for the purpose of accelerating the cleavage process and increasing the rate of deprotection. Wagner measures the efficacy of the groups for this purpose using HPLC of the crude oligonucleotide. The detection step of Wagner, therefore, occurs off the array, involves consumption of the biopolymer, and does not rely on fluorescence of the cleaved protecting group or any differential fluorescence whatsoever. Further, the methods of Wagner merely yield a cleavage (deprotection) reaction half-life and are not concerned with determining the completeness of the deprotection method. A reaction half-life as a parameter fails to provide any information on either the rate of deprotection at the end of the synthesis or the completeness of the deprotection. A person of ordinary skill in the art would understand that in the absence of characterization of the rate mechanics of the reaction as deprotection proceeds toward greater accumulation of the deprotection products, there is no way to extrapolate from a known half-life any information regarding completeness of the deprotection at the end of the synthesis.

Wagner merely teaches a method for deprotecting that enables use of a B-elimination reaction as the deprotecting mechanism and thereby achieves more rapid deprotection. Efficiency or completeness of deprotection using the detectable protecting group to determine a degree of deprotection of the end product is not taught or suggested by Wagner, and quality control of ***on-array*** or ***on-chip*** synthesis with respect to complete deprotection is not disclosed, addressed, or suggested.

As noted, anticipation under 35 USC §102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp.* 1 U.S.P.Q.2d at 1341. Further, it is well-established that to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). Wagner fails to disclose quality control methods comprising, inter alia, carrying out a determination of a detectable protecting group ***on the array*** after cleavage. The methods of Wagner rely on off-chip technologies for analysis of

the oligonucleotide product to determine a rate of deprotection. Hence, even if one might assume that the methods of Wagner, which are directed to rate determinations and not to overall completeness of the reaction, could be used to determine the latter, the Wagner methods could not do so without interfering with synthesis, removal of reagents from the array, and destruction of certain of the reagents. Since Wagner fails to disclose all the limitations of claim 1 and fails to disclose methods which could effectuate the purpose of the present invention as defined by claim 1, Wagner does not anticipate instant claim 1 or any claims dependent therefrom.

The rejection of claims 1-3 and 12-22 as being anticipated under 35 USC §102(b) by Wagner is therefore overcome. Reconsideration is respectfully requested.

Rejection under 35 USC §103

Claims 1-3 and 12-22 are rejected under 35 USC §103(a) as being unpatentable over Wagner in view of Hobbs et al., US 5,151,507 ("Hobbs") and, "if necessary," further in view of Chen et al., Journal of Organic Chemistry, Vol. 66:1725-1732, 2001, ("Chen"). Specifically, the Examiner applies Wagner for the disclosure set forth in the prior 102 rejection but notes that Wagner fails to teach "stilbene" as the fluorescent group as recited in claim 3. The Examiner asserts that Hobbs teaches the use of various fluorescent molecules "to label or protect" nucleotides and specifically teaches that stilbene can be used to attach to nucleobases through linkers comprising carbonyl groups, assertedly in accordance with instant claim 21, and generally teaches various fluorescent dyes which can be used depending on intended application. The secondary reference Chen is applied for the teaching that stilbene has a "bright fluorescence of very high quantum yield." The Examiner combines these reference teachings to conclude that it would have been *prima facie* obvious for one of ordinary skill in the art to attach a fluorescent group such as stilbene to a monomeric building block such as a nucleoside to form the detectable protecting group of the present invention, with a reasonable expectation of success for achieving the attachment since the references teach successful attachment of various fluorescent groups, including stilbene, to nucleosides through known reaction mechanisms. This rejection is traversed.

Independent claim 1, directed to quality control methods for manufacturing a biopolymer array, is set forth in detail above. In pertinent part, the method comprises carrying out a determination of the detectable protecting group on the array after cleavage in order to determine efficacy of deprotection.

Wagner, as noted above in response to the §102 rejection, discloses methods for determining a rate of deprotection but fails to teach or suggest methods for determining rates or quantifying

deprotection products that permit such determinations on the array as required by instant claim 1. The present invention provides superior quality control methods because it enables determination on the chip without interfering with synthesis of the biopolymer, without consuming the biopolymer product, and without requiring any additional post-determination steps. The methods of Wagner require removal of biopolymer and/or other reagents from the array and analysis by HPLC, which consumes some of the product. Wagner determines the rates of deprotection by halting the synthesis at various points and quantifying reagents across synthesis, which may be plotted to yield a curve from which a reaction half-life is obtained. The methods of Wagner reflect the inferior methods sought to be improved by the present methods, which enable on-chip analysis and which do not interfere with synthesis on the chip.

The secondary references do not overcome the deficiencies of Wagner. Hobbs is directed to certain labeled nucleotides useful as chain-terminating substrates for DNA sequencing and discloses the use of stilbene as one label. Hobbs fails to teach or suggest quality control methods applicable to biopolymer array synthesis and fails to disclose any methods comprising determination of detectable protecting groups on an array in order to determine efficacy of deprotection. Assuming there is a motivation to import the fluoreseing label stilbene of Hobbs into the methods of Wagner, the result is merely a different protecting group subject to the same off-chip HPLC analysis of Wagner, and the combination fails to achieve the present inventive methods which are concerned, inter alia, with the quality of the biopolymer array at the end of synthesis. The secondary reference Chen, directed to the properties of stilbene as a fluorescent label, is completely inapposite to overcoming the deficiencies of Wagner.

To establish *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). The combination of Wagner, Hobbs, and Chen fails to teach or suggest quality control methods for manufacturing a biopolymer array that are capable of being performed **on the array** without interfering with the synthesis of the biopolymer array and without additional steps required after carrying out the quality control step of determining efficacy of deprotection. The methods of Wagner, taken with the teachings of Hobbs and Chen regarding labels, do not enable the present inventive methods, as Wagner subjects the oligonucleotides and deprotection products to analysis via HPLC and never suggests analytical technology that enables determination on the array. The present inventive methods, as opposed to the method resulting from the combination of references as asserted by the Examiner, assess quality of

the array at the end of synthesis, do not interfere with synthesis, and do not require any further processing of the array before it may be used in subsequent applications.

Hence, the rejection of claim 1 and claims 2, 3, and 12-22 dependent therefrom as being unpatentable under 35 USC §103 over Wagner in view of Hobbs and Chen is overcome. Reconsideration is respectfully requested.

Conclusion

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3, 12, 13, and 15-22 at an early date is earnestly solicited.

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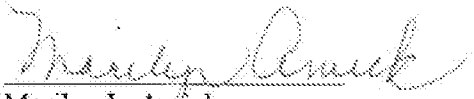
The Commissioner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958.

Respectfully submitted,



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